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Review Article

Cancer metabolism: New insights into classic characteristics

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Summary Initial studies of cancer metabolism in the early 1920s found that cancer cells were phenotypically characterized by aerobic glycolysis, in that these cells favor glucose uptake and lactate production, even in the presence of oxygen. This property, called the Warburg effect, is considered a hallmark of cancer. The mechanism by which these cells acquire aerobic glycolysis has been uncovered. Acidic extracellular fluid, secreted by cancer cells, induces a malignant phenotype, including invasion and metastasis. Cancer cells survival depends on a critical balance of redox status, which is regulated by amino acid metabolism. Glutamine is extremely important for oxidative phosphorylation and redox regulation. Cells highly dependent on glutamine and that cannot survive with glutamine are called glutamine-addicted cells. Metabolic reprogramming has been observed in cancer stem cells, which have the property of self-renewal and are resistant to chemotherapy and radiotherapy. These findings suggest that studies of cancer metabolism can reveal methods of preventing cancer recurrence and metastasis.

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1. Introduction

Initial studies of cancer metabolism in the early 1920s showed that the cancer phenotype for glucose metabolism is unique, with increased abilities to take up glucose and produce lactate, even under aerobic conditions [1]. This pathway, called aerobic glycolysis or the Warburg effect, results in extracellular fluid around tumor tissue having acidic pH [1,2]. Indeed, the extracellular pH (pH_e) of most tumor tissues is around 6.5—6.9, and may be even lower (*e.g.*, 5.7) in some cases [3—5]. However, despite lactate production by tumor tissue, blood lactate level is often unaffected [6], suggesting that acidity is limited locally to the microenvironment around tumor tissue.

Accumulated evidence about cancer phenotypes has indicated that all cancers have in common six biological capabilities acquired during multistep development: sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, replicative immortality, induction of angiogenesis, and activation of invasion and metastasis [7]. Later research has revealed two additional hallmarks of cancer: reprogrammed energy metabolism and evasion of immune-mediated destruction [8]. Recent studies have shown that metabolic reprogramming regulates cancer stemness [9]. Thus, ''cancer metabolism'' has again become an important research topic. Here, we focus on glucose and glutamine metabolism.

2. Glucose metabolism and its regulation

2.1. Hypoxia

Tumor cells utilize glycolysis to supply energy, even under aerobic conditions, resulting in the conversion of pyruvate to lactate in the extracellular space. Hypoxia stimulates lactate production in tumors by activating hypoxia-inducible transcription factor 1α (HIF1α)-dependent expression of genes such as glucose transporter 1 (GLUT1), hexokinase 2 (HK2), pyruvate kinase (PK) M2, pyruvate dehydrogenase kinase 1 (PDK1), enolase 1 (ENO1), and lactate dehydrogenase A (LDHA) [10—15] (Fig. 1). LDHA converts pyruvate to lactate and PDK1 inhibits pyruvate dehydrogenase (PDH), which converts pyruvate to acetyl-CoA to produce ATP by mitochondrial oxidative phosphorylation (OXPHOS) [11,16—18]. This pathway facilitates lactate production rather than OXPHOS. Hypoxia also induces the expression of monocarboxylate transporter 4 (MCT4), which functions as a proton-coupled transporter of lactate across cell membranes [19,20]. Thus, hypoxia enhances the Warburg effect, which is responsible for high lactate secretion by tumor cells.

2.2. Histone deacetylases (HDACs)

Sirtuins, which are mammalian homologs of the yeast histone deacetylase Sir2, are NAD^+-dependent HDACs and consist of seven isoforms (SIRT1—7). These enzymes are involved

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